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Signature Jay R Akhave *Date* 9.14.04

13 September, 2004

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Alexandria
VA 22313-1450

Sub: Certified Foreign Priority Document on U.S. Application 10/648,636

Dear Sir:

This is a submission of certified priority documents for the following U.S. Patent application.

U S Patent Application No.	10/648,636
Filing Date	8/26/2003
Title	A process for preparing 1-methyl-3-phenylpiperazine using a novel intermediate
First named Inventor	Vijay Kumar Handa
Art Unit	1624
Attorney Docket No.	2003-016
Filing Status	Filed awaiting First office Action

Sincerely,
Jay R Akhave
Jay Akhave
845 Pomello Dr
Claremont CA 91711
909 625 3492
US Patent Agent No 50,016

Encl: Certified Copy of Indian Application No. 442/MAS/2003

THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application, Complete Specification & Abstract of the extract of Patent Application No.442/MAS/2003, dated 02/06/2003 by M/s.Aurobindo Pharma Limited having its registered office at Plot No.2, Maitrivihar Complex, Ameerpet, Hyderabad – 500 038, Andhra Pradesh, India.

.....

.....In witness thereof

I have hereunto set my hand

Dated this the 8th day of July 2004

M.S. Venkataraman

(M.S. VENKATARAMAN)
Assistant Controller of Patents & Designs

PATE[illegible]OF[illegible]CE BRANCH
GOVE[illegible]ME[illegible]OF INDIA
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THE PATENTS ACT, 1970

1442/MAS/03
2.6.03

- 8 DEC 2003

ORIGINAL

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)
APPLICATION FOR GRANT OF A PATENT OFFICE
[See section 5(2), 7/54 and 135]

1. We

AUROBINDO PHARMA LIMITED
PLOT NO. 2, MAITRIVIHAR COMPLEX (Regd. Office)
AMEERPET
ANDHRA PRADESH
HYDERABAD – 500 038
INDIA
(AN INDIAN ORGANISATION)

2. Hereby declare: -

(a) That we are in possession of an invention titled: -

"A PROCESS FOR PREPARING 1-METHYL-3-PHENYLPIPERAZINE."

(c) That the Complete Specification relating to this invention is filed with this application.

(d) That there is no lawful ground of objection to grant of a Patent to us.

3. Further declare that the inventor(s) for the said invention is: -

(a) **VIJAY KUMAR HANDA**

(b) **DIVVELA VENKATA NAGA SRINIVASA RAO**

(c) **MEENAKSHISUNDERAM SIVAKUMARAN**

C/o. AUROBINDO PHARMA LIMITED
PLOT NO. 2, MAITRIVIHAR COMPLEX (Regd. Office)
AMEERPET
ANDHRA PRADESH
HYDERABAD – 500 038.
INDIA

(a) to (c) : **CITIZENS OF INDIA**

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows:-

(a) NIL

(b) NONE

5. We state that the said invention is an improvement in or modification of the particulars of which are as follows and of which we are the Applicant/Patentee:

(a) NIL

(b) NONE

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application be deemed to have been filed on .... under section 16 of the Act:

NONE

7. That we are the assignee or legal representative of the true and first Inventors.

8. That our addresses for service in India is as follows:

AUROBINDO PHARMA LIMITED
Plot No. 2, Maitrivihar Complex,
Ameerpet,
Andhra Pradesh
Hyderabad - 500 038
India
Phone No.: 91-40-23741083
Fax No. : 91-40-23741080, 23740591

9. Following declaration was given by the inventor(s) or applicant(s) in the convention country:-

We the true and first inventors for the invention, declare that the applicant(s) herein are our assignee:

(a) VIJAY KUMAR HANDA Vijay Kumar Handa

(b) DIVVELA VENKATA NAGA SRINIVASA RAO

(c) MEENAKSHISUNDERAM SIVAKUMARAN

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct ad that there is no lawful ground of objection to the grant of patent to us on this application.

11. Following are the attachment with the application: -

(a) Complete Specification (triplicate)

(b) Drawings Nil

(c) Priority document(s)

(d) Fee Rs. 5000/- in Bank Draft bearing No..... dated 1-06-03 on State Bank of Hyderabad.

We request that a Patent may be granted to us for the said invention.

Dated this 30th day of May 2003.

AUROBINDO PHARMA LTD. HYDERABAD INDIA

(Dr M. SIVAKUMARAN)
DIRECTOR

TO
THE CONTROLLER OF PATENTS,
THE PATENT OFFICE,
CHENNAI

Form-2

THE PATENT ACT, 1970

COMPLETE

SPECIFICATION

(SECTION 10)

TITLE

"A PROCESS FOR PREPARING 1-METHYL-3-PHENYLPIPERAZINE"

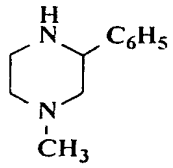
APPLICANT

AUROBINDO PHARMA LIMITED
HAVING REGISTERED OFFICE AT
PLOT NO. 2, MAITRI VIHAR COMPLEX,
AMEERPET, HYDERABAD – 500 038,
ANDHRA PRADESH, INDIA,
AN INDIAN ORGANIZATION

The following specification particularly describes and ascertains the nature of this invention and the manner in which the same is to be performed.

FIELD OF THE INVENTION

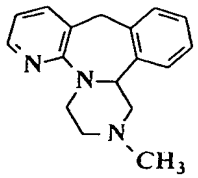
The present invention relates to the process for preparing 1-methyl-3-phenylpiperazine of Formula I from 4-benzyl-1-methyl-2-oxo-3-phenylpiperazine.



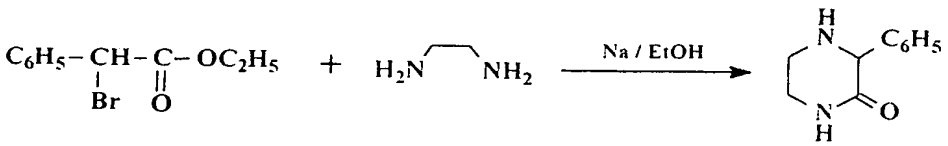
Formula I

BACKGROUND OF THE INVENTION

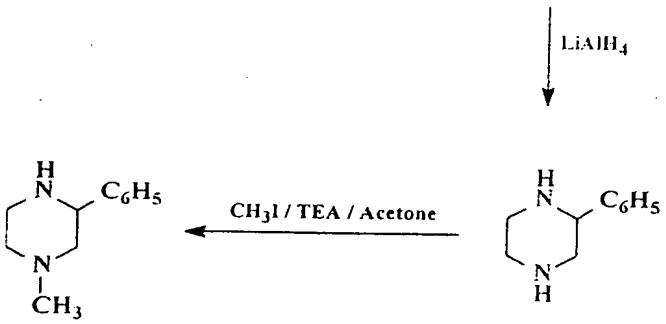
Mirtazapine, also known as 2-methyl-1,2,3,4,10,14b-hexahydrobenzo[c]pyrazino-(1,2-a) pyrido[3,2-f]azepine, is an antidepressant drug suitable for oral administration. Mirtazapine belongs to piperazinoazepine group of compounds and has the following chemical structure.



1-Methyl-3-phenylpiperazine is the key intermediate in the preparation of Mirtazapine. US Patent 4,062,848 has described the synthesis of Mirtazapine using 1-methyl-3-phenylpiperazine as starting material. It is believed that the earliest synthesis of this key intermediate is that of Roderick et. al., J. Med. Chem. 1966, 181-185. This publication has reported the preparation of 1-methyl 3-phenylpiperazine starting from α-bromophenylacetic acid ester and ethylenediamine resulting in the formation of 2-oxo-3-phenylpiperazine, which is then subjected to lithium aluminium hydride reduction and subsequently methylated with methyl iodide and triethylamine in acetone.

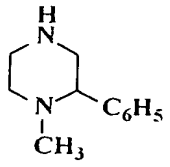


ETHYL α-BROMOPHENYLACETATE *ETHYLENEDIAMINE* *2-OXO-3-PHENYLPIPERAZINE*

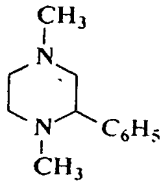


1-METHYL-3-PHENEYLPIPERAZINE *2-PHENEYLPIPERAZINE*

The drawback of this method is the non-selective methylation at 1-position. A mixture of products like unreacted 2-phenylpiperazine, 1-methyl-2-phenylpiperazine and 1,4-dimethyl-2-phenylpiperazine alongwith the desired 1-methyl-3-phenylpiperazine is obtained. Therefore, extensive purification is required to obtain pure 1-methyl-3-phenylpiperazine.

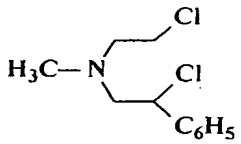


1-METHYL-2-PHENYLPIPERAZINE



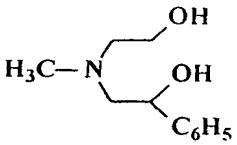
1,4-DIMETHYL-2-PHENYLPIPERAZINE

US Patent 6,495,685 has described the preparation of 1-methyl-3-phenylpiperazine by reacting *N*-(2-chloroethyl)-*N*-methyl-β-chloro-β-phenylethylamine (the dichloride) of Formula III with ammonia.



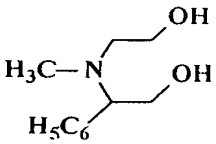
Formula III

This dichloride of Formula III has been prepared by chlorination of the corresponding diol, *N*-(2-hydroxyethyl)-*N*-methyl-β-hydroxy-β-phenylethylamine of Formula IV.



Formula IV

In US Patent 6,495,685, this diol has been obtained by reacting styrene oxide with *N*-methylethanolamine. However, the described preparation of diol results in the formation of substantial amount of isomeric compound of Formula V due to non-selectivity in this reaction.



Formula V

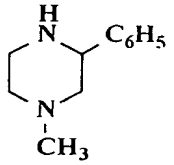
The presence of isomeric diol of Formula V results in the formation of corresponding 1-methyl-2-phenylpiperazine isomer, which contaminates the product and results in lower productivity.

Next, the same dichloride of Formula III has been treated with *p*-toluenesulfonamide in the US Patent 6,339,156 to obtain tosyl piperazine, which is hydrolyzed to produce 1-methyl-3-phenylpiperazine. However, preparation of dichloride and its isomeric purity has not been discussed in this US Patent.

In view of the prior art described above, the present invention provides a new process for preparing highly pure 1-methyl-3-phenylpiperazine where the formation of 2-phenylpiperazine, 1-methyl-2-phenylpiperazine isomer and 1,4-dimethyl-2-phenylpiperazine has been avoided.

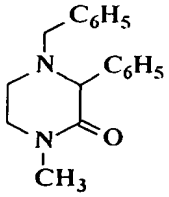
SUMMARY OF THE INVENTION

The present invention relates to a process for preparing 1-methyl-3-phenylpiperazine represented by Formula I



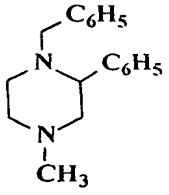
Formula I

which comprises the steps of ,
reducing the compound of Formula II



Formula II

with lithium aluminium hydride to prepare compound of Formula VII



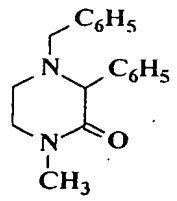
Formula VII

and deprotecting the compound of Formula VII by hydrogenation in acetic acid in the presence of palladium-carbon catalyst.

DETAILED DESCRIPTION OF THE INVENTION

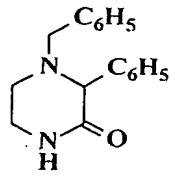
The present invention relates to a new process for preparing highly pure 1-methyl-3-phenylpiperazine suitable for use in the synthesis of Mirtazapine and other tetracyclic compounds. The present invention also relates to a novel intermediate used to carryout this process.

According to the present invention, there is provided a process for preparing a novel compound, 4-benzyl-1-methyl-2-oxo-3-phenylpiperazine, of Formula II



Formula II

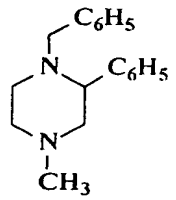
by methylation of 4-benzyl-2-oxo-3-phenylpiperazine of Formula VI



Formula VI

with methyl iodide in *N,N*-dimethylformamide in presence of sodium hydride. Typically, the methylation is carried out with 1.1 to 1.2 moles of methyl iodide and sodium hydride each per one mole of compound of Formula VI. It is preferred to carryout the methylation by adding compound of Formula VI to the sodium hydride slurry in *N,N*-dimethylformamide followed by methyl iodide addition. The temperature during methylation is maintained at 10°C to 25°C and usually it takes 1 hour to complete the reaction.

Reduction of the above mentioned novel piperazine compound is carried out with lithium aluminium hydride in tetrahydrofuran to obtain protected piperazine of Formula VII.



Formula VII

This reduction is accomplished with 1.0-1.2 mole of lithium aluminium hydride per mole of the compound of Formula VI at a temperature 40°C to 70°C and preferably at the reflux temperature.

Finally, 1-methyl-3-phenylpiperazine of Formula I is obtained by removing benzyl protecting group through catalytic hydrogenation. The deprotection is performed by dissolving the compound of Formula VII in acetic acid and subjecting it to hydrogenation at 20°C to 30°C in the presence of 5% palladium-carbon catalyst. The hydrogen pressure is maintained at 80 psi to 100 psi. End point of the reaction is readily confirmed by high performance liquid chromatography and thereafter acetic acid is removed by distillation. An aqueous alkali such as sodium hydroxide is added to the reaction mass containing 1-methyl-3-phenylpiperazine of Formula I thus obtained to make the solution alkaline, for instance, to pH 11.0 to 12.0. 1-Methyl-3-phenylpiperazine can be isolated by extracting with toluene, methylene chloride, ethyl acetate, cyclohexane or the like, preferably with toluene and thereafter distilling the extract.

The major advantage of the present invention is that 1-methyl-3-phenylpiperazine thus obtained contains none of the impurities like 2-phenylpiperazine, 1-methyl-2-phenylpiperazine isomer and 1,4-dimethyl-2-phenylpiperazine.

1-Methyl-3-phenylpiperazine as obtained by the method described in this invention can be used in the preparation of Mirtazapine.

The invention is further illustrated by the following examples.

Example 1

PREPARATION OF 4-BENZYL-1-METHYL-2-OXO-3-PHENYLPIPERAZINE

15.3 g of sodium hydride (65% dispersion in mineral oil, 0.414 moles) was suspended in 250 ml of *N,N*-dimethylformamide at 10°C. To this suspension, 100 g of 4-benzyl-2-oxo-3-phenylpiperazine (0.376 moles) was added portionwise over a period of 30 min and stirred for 15 min. A solution of 64 g of methyl iodide (0.45 moles) in 50 ml of *N,N*-dimethylformamide was added slowly in 45 min maintaining the temperature below 25°C and maintained for 1 hour. After completion of the reaction, mass was poured slowly in 1000 ml of cold water (15°C). The product was extracted with toluene (1x500 ml, 1x300 ml) from aqueous phase. Toluene layer was washed with water (2x200 ml) and concentrated. To the residue, 250 ml of cyclohexane was added and cooled to 10°C with stirring. Filtered the product and washed with pre-cooled cyclohexane to obtain 98.5 g of 4-benzyl-1-methyl-2-oxo-3-phenylpiperazine product (yield: 93.8%, purity: 99.15 by HPLC)

MASS : m/z; 281.0 $[(MH)^+]$

^{1}H NMR (300 MHz) in *$CDCl_3$* : *δ(ppm)*; 2.49-2.57 (*m*, 1H), 2.97 (*s*, 3H),
2.99-3.03 (*m*, 1H), 3.14-3.18 (*m*, 2H),
3.54-3.77 (*m*, 2H), 4.06 (*s*, 1H),
7.21-7.53 (*m*, 10H).

Example 2

PREPARATION OF 4-BENZYL-1-METHYL-3-PHENYLPIPERAZINE

14.62 g of lithium aluminium hydride (0.385 moles) was suspended in 450 ml of tetrahydrofuran at 15°C under nitrogen atmosphere. 90 g of 4-benzyl-1-methyl-2-oxo-3-phenylpiperazine (0.321 moles) was added slowly in 1 hour at 10-15°C. The reaction mass was refluxed for 6 hours. Thereafter, the reaction mass was cooled to 5°C and quenched successively with 15 ml of water, 15 ml of 15% aqueous sodium hydroxide solution, 45 ml of water. The reaction mass was stirred for 1 hour at 20-25°C, filtered and residue was washed with tetrahydrofuran (2x90 ml). The filtrate was concentrated and 300 ml of water was added. Filtered the product, washed with water and dried under reduced pressure to obtain 80 g of the title compound (yield: 93.6%).

^{1}H NMR (300 MHz) in $CDCl_3$: δ(ppm); 2.08-2.24 (*m*, 3H), 2.27 (*s*, 3H),
2.73-2.88 (*m*, 4H),
3.39-3.44 (*m*, 1H), 3.79-3.83 (*m*, 1H),
7.17-7.50 (*m*, 10H).

PREPARATION OF 1-METHYL-3-PHENYLPIPERAZINE

60 g of 4-benzyl-1-methyl-3-phenylpiperazine (0.226 moles) obtained above was dissolved in acetic acid (300 ml) and 3 g of 5% palladium on charcoal (50% wet) was added and the reaction mass was subjected to hydrogenation at 80-100 psi for 4 hours at 25-30°C. After completion of the reaction by HPLC, the reaction mixture was filtered and acetic acid was concentrated under reduced pressure. 150 ml of water was added to dissolve the residue and washed with 60 ml of toluene. pH was adjusted to 11.0-12.0 with 50% sodium hydroxide solution and the product was extracted with toluene (1x300 ml, 1x180 ml). Toluene was concentrated under

reduced pressure and highly pure title compound was isolated in cyclohexane (80 ml, 10°C) having HPLC purity 100%.

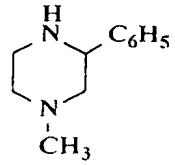
m.p.: 58-60°C

MASS : m/z; 177.0 [$(MH)^+$]

^{1}H NMR (300 MHz) in $CDCl_3$: *δ(ppm)*; 1.76 (*bs*, 1H), 1.93-2.16 (*m*, 2H), 2.29 (*s*, 3H), 2.76-3.07 (*m*, 4H), 3.85-3.86 (*m*, 1H), 7.21-7.39 (*m*, 5H).

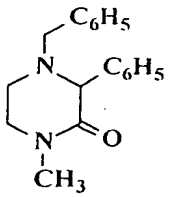
WE CLAIM:

1. A process for preparing 1-methyl-3-phenylpiperazine represented by Formula I



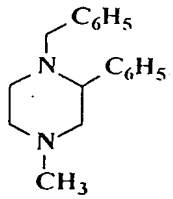
Formula I

which comprises the steps of ,
reducing the compound of Formula II



Formula II

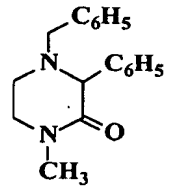
with lithium aluminium hydride to prepare compound of Formula VII



Formula VII

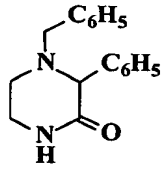
and deprotecting the compound of Formula VII by hydrogenation in acetic acid in the presence of palladium-carbon catalyst.

2. The process according to claim 1, wherein compound of Formula II



Formula II

is prepared by the process comprising methylation of compound, 4-benzyl-2-oxo-3-phenylpiperazine, of Formula VI



Formula VI

with methyl iodide in *N,N*-dimethylformamide in the presence of sodium hydride.

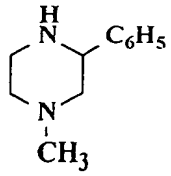
Dated this the 30th day of May 2003

AUROBINDO PHARMA LIMITED,

Dr. M. SIVAKUMARAN,
DIRECTOR.

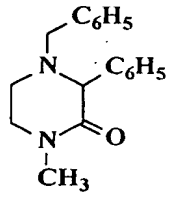
ABSTRACT

The present invention describes an industrially advantageous process to prepare highly pure 1-methyl-3-phenylpiperazine of Formula I



Formula I

that makes use of a novel piperazine derivative, 4-benzyl-1-methyl-2-oxo-3-phenylpiperazine, represented by Formula II



Formula II

The process to prepare compound of Formula II is also disclosed.

1-Methyl-3-phenylpiperazine is a useful intermediate in the preparation of antidepressant Mirtazapine.

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